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Association between illicit drug and alcohol use and first manic episode

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Abstract

In light of the established influence of substance use on the onset, course, and outcome of bipolar disorder, we performed a retrospective chart review of patients with bipolar I disorder participating in a randomized controlled trial to further investigate the relationship between alcohol and substance use and first onset of mania. A total of 59.4% (N=101) of the 170 participants were determined to have a history of substance and/or alcohol use. Among the 101 participants with SU, use was coded in 10 (9.9%) as immediately preceding, in 50 (49.5%) as preceding mania, in 7 (6.9%) as following mania, and in 34 (33.7%) as indeterminable. Of the 10 participants with *immediately preceding* use, 5 experienced their first manic episode immediately after *discontinuing* a substance. Our findings support earlier reports detailing the high prevalence of substance use among patients with bipolar disorder. Treatments targeting alcohol and substance use among individuals with bipolar disorder are clearly needed, as are prophylactic treatments targeting adolescents and young adults who are at risk for either bipolar disorder or alcohol and substance related disorders.

Keywords: Substance use; Manic episode; Illness onset; Bipolar disorder

1. Introduction

Compared to the general US population, individuals with bipolar disorder (BP) are at increased risk for substance use (SU) disorders. SU disorders vary in severity and include disorders manifesting from an individual's use of a drug of abuse or alcohol (APA, 2000). According to findings from the Epidemiologic Catchment Area study, SU disorders are the most common Axis I comorbidity among individuals with BP. As many as 60% of individuals with bipolar I disorder will develop a SU disorder during their lifetime (Regier et al., 1990). Individuals with early onset BP may be especially at risk (Bashir et al., 1987; Perlis et al., 2004; Lin et al. 2006; Fossey et al., 2006).

Mood and SU disorders are associated with substantial distress, disability, and burden and hinder social and occupational functioning (Levin and Hennessy, 2004; Woods, 2000). Results from the National Comorbidity Survey (NCS) revealed that mania is more closely tied to lifetime and 12-month substance dependence than any other mood or anxiety disorder (Kessler et al., 1996). The effects of substance use among individuals with bipolar disorder may be especially dire. Researchers have found a negative association among habitual and even interval, alcohol and substance use and age of illness onset, illness course, and treatment outcome Cassidy et al., 2001; Haywood et al., 1995; Kessler et al., 1996; Levin and Hennessy, 2004; Strakowski et al., 1996, 1998, 2000a,b, 2005). For instance, cumulative findings by Strakowski et al. (1996, 1998, 2000a,b) demonstrate that, compared to individuals with BP and no alcohol or substance use, individuals with BP who use alcohol and/or illicit substances (excluding cannabis) have (1) higher rates of hospitalizations, (2) lower rates of remission during hospitalizations, (3) are more likely to experience mixed episodes, rapid mood cycling, persistent mood symptoms with treatment, and residual symptoms during recovery, and (4) are more likely to be poor or non-responders to lithium. Also of note, findings by Strakowski et al. (2000a,b) suggest that initiation of illicit substance use among individuals with BP after onset of first mania is rare and, among individuals with BP who use cannabis, the duration of cannabis use is highly correlated with the duration of mania.

In a study investigating the relationship between BP and alcohol use only, Strakowski et al. (2005) found that alcohol use was strongly associated with the maintenance or emergence of mood symptoms. Compared to individuals with concurrent or no

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alcohol use, individuals with antecedent alcohol use exhibited a clinical phenotype consistent with a less severe manifestation of BP, had lower familial rates of BP, and had a later age of illness onset, suggesting alcohol use may have played a role in BP onset. Different studies (Weissman et al., 1984; Strober et al., 1988; Somanath et al., 2002; Lin et al., 2006) suggested the genetic heterogeneity of BP noting a familial aggregation between the age at onset and alcohol and drug abuse.

Strakowski et al., (2000a,b) review three hypotheses that researchers have proposed to explain the high prevalence of comorbid SU and BP. On one hand, SU and BP comorbidity may increase treatment-seeking behavior. Accordingly, individuals who suffer from an alcohol and/or substance use (AU/SU) disorder and BP experience more symptoms than individuals with only an alcohol use AU/SU or mood disorder, so these individuals seek treatment more often. This hypothesis, known as Berkson's or ascertainment bias, is unlikely to be true since AU/SU and BP comorbidity rates are elevated in non-clinical populations as well.

On the other hand, diagnostic biases may explain the high prevalence of AU/SU and BP. Diagnosticians may code an individuals' alcohol and substance use as "high involvement in pleasurable activities." Consequently, this use contributes to the diagnostic criteria for both a manic episode and a substance disorder. This hypothesis also is unlikely to be true since individuals with comorbid AU/SU and BP exhibit longitudinal alcohol and substance use characteristics.

A third hypothesis postulates that the variable, but high co-occurrence of AU/SU and BP results from various interactions between AU/SU and bipolar disorder and vary from person-to-person. Some individuals may attempt to self-medicate with, or use alcohol and substances as a consequence of mania. For others, substance abuse may initiate affective episodes via behavioral sensitization or kindling. For a third group of individuals, the co-occurrence may be a result of common risk factors for both disorders. Strakowski et al. (2000a,b) believe that this hypothesis is the most likely explanation and fits the data best; however, to understand the complex relationship between AU/SU and BP, more systematic studies are needed.

In light of the established influence of alcohol and substance use on the onset, course, and outcome of BP, we performed a retrospective chart review of patients with bipolar I disorder participating in a randomized controlled trial in order to further investigate the association between alcohol and substance use and first onset of mania in a population of participants who reported no AU/SU disorder in the past 5 years. Because our study was conducted on a sample of participants who did not currently meet criteria for an alcohol or substance abuse disorder, we were also interested in subsyndromal use of illicit substances and its relationship to onset of mania.

2. Materials and methods

2.1. Subjects

Our sample consists of 154 participants in the Maintenance Therapies for Bipolar Disorder (MTBD) protocol (Frank et al., 2005), and 8 participants from a supplemental study to the MTBD protocol designed to examine the efficacy of interpersonal and social rhythm therapy (IPSRT — Frank, 2005) in individuals who met full criteria for bipolar I disorder and full criteria for borderline personality disorder (Swartz et al., 2005). Another 8 participants who were screened for MTBD and had a diagnosis of bipolar I disorder, but did not enter into the study because they did not complete their first treatment visit were also included for a total $N=170$. We were able to obtain initial evaluation data on these 8 participants for the purposes of our chart review. One-hundred and one were women and 69 were men; 10% identified as non-Caucasian, and 35% were married. The mean age at entry was 35 years (SD=9.9), and the mean years of education was 14.9 (SD=1.9). At study entry, 90 participants were experiencing a depressive episode, 35 were experiencing a manic episode, and 39 were experiencing a mixed/cycling episode. Data on episode polarity were missing for 6 of the 8 subjects who did not enter the MTBD study. The median number of previous episodes was 6. Mean duration of index episode was 35.4 (SD=58.8) weeks. We report additional clinical characteristics of the study population in Table 1.

2.2. Study design

Full details of the study design, inclusion and exclusion criteria, and instruments can be found in the primary report from this trial (Frank et al., 2005). Briefly, the MTBD protocol was a randomized controlled trial comparing two psychosocial interventions for patients with bipolar I disorder: interpersonal and social rhythm therapy (IPSRT) (Frank, 2005) and intensive clinical management (ICM), an adaptation of the clinical management strategy used in the National Institute of Mental Health treatment of Depression Collaborative Research Program (Elkin et al., 1989).

To enter the MTBD protocol, participants were required to have (1) a lifetime diagnosis of bipolar I disorder (confirmed by a Structured Clinical Interview for DSM-IV-Patient Version interview (SCID; First et al., 1995)); (2) be experiencing at least their third affective episode, with the most recent episode being within 5 years from the index episode; and (3) be between 18 and 65 years old. Exclusion criteria for the main study included rapid cycling, chronic alcohol or substance abuse during the

Table 1
Clinical characteristics of study population ($N=170$)

	Mean (SD)	Median
Age at onset of first depressive episode	22.1 (7.8)	20
Age at onset of first manic episode	25.1 (8.4)	23
Number of prior episodes		
Depressive	5.6 (6.8)	4
Manic	4.0 (4.7)	3
Duration of index episode (weeks)	35.4 (58.8)	19
Baseline HDRS 17-item ($n=90$, depressed)	19.5 (4.5)	18
Baseline Bech–Rafaelsen Mania Scale ($n=35$, manic)	26.4 (8.1)	24
Baseline HDRS 17-item ($n=39$, mixed-cycling)	15.1 (8.2)	16
Baseline Bech–Rafaelsen Mania Scale ($n=39$, mixed-cycling)	14.5 (12.7)	14
Global Assessment Scale	48.2 (9.0)	50

previous 5 years, meeting full criteria for borderline or antisocial personality disorder, unstable severe medical conditions, and pregnancy. Exclusion criteria for the supplemental study on patients with comorbid borderline personality disorder (BPD) were identical, with the exception of the presence of BPD.

The University of Pittsburgh's biomedical institutional review board approved all recruitment, assessment, and treatment procedures (IRB #950310). Potential participants provided written informed consent after being provided with a complete description of the study and an opportunity to ask questions.

2.3. Procedure

Study evaluators completed intake psychiatric evaluations (Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer, 1978), Research Diagnostic Criteria (RDC; Spitzer et al., 1978) and/or SCID-I, -II), symptom assessment, and, when possible, life chart data in accordance with the National Institute of Mental Health Life Charting Protocol (Leverich and Post, 1997).

To obtain data on lifetime history of substance use, we utilized NIMH Life Charting Protocols, when available (N=116), and participants' initial psychiatric evaluations (N=54). Because the life chart offers specific onset and offset dates for episodes, we determined age of first onset of mania by calculating the subject's age at the date of the first onset indicated on the chart. Because there were several subjects whose first recorded mania occurred prior to hospitalization, we opted not to use first hospitalization as an indicator of onset of mania. Each instance of substance use recorded in the charts was noted and categorized based on the time between use and first onset of mania. We operationally defined *immediately preceding* as use occurring in the 3 weeks before first onset of mania, *preceding* as any antecedent use up to the 3 weeks before first onset of mania, and *following* as use occurring after onset of mania, and *indeterminable* as when the relationship between use and mania onset could not be determined. We chose a 3 week window for the *immediately preceding* group in order to allow for enough time for manic symptoms to become severe enough to become apparent and/or warrant the seeking of treatment. Substances found in our review of use included alcohol and illicit drugs such as marijuana, cocaine, opiates, amphetamines, prescription pain medications, and benzodiazepines.

2.4. Rating scales

The NIMH Life Charting method (Leverich and Post, 1997) is a semi-structured assessment used to evaluate longitudinal mood symptoms and functioning. This clinician-administered interview yields information on frequency and severity of episodes, episode onset and offset dates, treatment response, medication and substance use history, and major life events.

The Psychiatric Evaluation Form (PEF) is a semi-structured interview used at Western Psychiatric Institute and Clinic to gather information on patient background, history of present illness, past psychiatric history, suicidal/homicidal ideation and behavior, past and present substance use, religious, military, and social history, and assessment of functioning. Also included in the evaluation is an assessment of the patient's present mood and affect, cognitive functioning, perception, and insight into present illness.

Diagnostic determinations were made using the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer, 1978), and, after 1995, the Structured Clinical Interview for DSM-IV-Patient Version (SCID; First et al., 1995). Presence of an affective episode was confirmed at study entry and at point of recurrence using the Research Diagnostic Criteria (RDC; Spitzer et al., 1978) for all study subjects.

Severity of index episode was determined using the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) for depression and the Bech–Rafaelsen Mania Scale (BRMS; Bech et al., 1979) for mania or mixed episodes. The HDRS is a 17-item rating scale that assesses mood, vegetative and cognitive symptoms of depression, as well as comorbid anxiety symptoms (Hamilton, 1960). It has been a gold standard for the assessment of depression for more than 40 years (see Hedlund et al., 1979 for a review of its psychometric properties). The Bech–Rafaelsen Mania Scale is an 11-item scale that evaluates symptoms of mania and hypomania such as elevated mood, pressure of speech, increased social contact, increased motor activity, sleep disturbances, social activities and distractibility, hostility and irritability, and increased sexual activity (Bech et al., 1979). The inter-observer reliability of this scale has been found to be high in a number of studies conducted in various countries. The Bech–Rafaelsen Mania Scale has shown acceptable external validity, in terms of both sensitivity and responsiveness (Bech, 2002).

2.5. Data analysis

Descriptive statistics are provided for the prevalence of substance and alcohol use within the sample. Subjects with and without substance use were compared using the chi-square test for categorical variables and the t-test or the Mann–Whitney test for continuous variables, as appropriate.

The same tests were used for comparing the characteristics of subjects with substance use that developed before (or immediately before) the onset of bipolar disorder (*primary substance use*) and subjects with substance use that developed after (or probably after) bipolar disorder (*secondary substance use*). The alpha level was set at 0.05 for the primary comparison (substance use vs. no substance use) and 0.01 for secondary comparisons involving subgroups of subjects with substance use to minimize the risk of type-I error. SPSS, version 12.0 was used to perform these analyses.

3. Results

3.1. Clinical characteristics and effects of substance drug use

A total of 59.4% (N=101) of the 170 study subjects were determined to have a history of substance and/or alcohol use.

Comparison of the demographic and clinical features of subjects with and without substance use indicated no difference

Table 2
Specific substances used ($N=101$)

Category	Immediately preceding or (immediately after discontinuing)[a] ($N=10$)	Preceding ($N=50$)	Following ($N=7$)	Indeterminable ($N=34$)
Alcohol	6 (1)[a] (60%)	30 (60%)	4 (57%)	26 (76%)
Cannabis	4 (2)[a] (40%)	28 (56%)	3 (43%)	14 (41%)
Pain killers	3 (2)[a] (30%)	0	2 (29%)	0
Opiates	0	1 (2%)	0	1 (3%)
Barbiturates	0	1 (2%)	0	0
Amphetamines	0	6 (12%)	0	5 (15%)
Cocaine	1 (10%)	7 (14%)	2 (29%)	5(15%)
Polysubstance	2 (20%)	25 (50%)	3 (43%)	12 (35%)

[a] The participants in parentheses here had their first manic episode immediately after *discontinuing* substance use.

between groups on gender, mean age, educational level, onset of bipolar disorder, number of previous manic episodes. However, there was a significant difference between groups on the number of depressive episodes (median=6 in the group with AU/SU and median=3 in the group without AU/SU, Mann–Whitney test, $p=0.001$). There was also a significant difference in functioning at study entry, with substance users having better functioning (49.5±8.8 vs. 46.0±9.0, t-test=2.2, $p=0.027$). However, it should be noted that the mean score of both groups is within the range of severe functional impairment (41 to 50).

In the 101 participants with AU/SU, use was coded in 10 (9.9%) as immediately preceding, 50 (49.5%) as preceding mania, 7 (6.9%) as following mania, and 34 (33.7%) as indeterminable. Of the 10 participants with immediately preceding use, 5 experienced their first manic episode immediately after *discontinuing* alcohol or substance use. Substance use plus alcohol use occurred in 42 (41.6%) of the 101 substance-using participants.

Secondary AU/SU was associated with an earlier onset of bipolar disorder (mean age=18.9 vs. 21.8, t-test=−2.1, $p=0.036$) and a higher number of manic episodes (median 3.5 vs. 3, Mann–Whitney test, $p=0.047$) than primary substance use. These differences however fail to reach the significance level of 0.025. No other comparison between these two groups on demographic or clinical variables was significant. Details of specific substances used are provided in Table 2.

4. Discussion

Researchers have consistently found that individuals with bipolar disorder are at increased risk for alcohol and substance related disorders (Kessler et al., 1996; Levin and Hennessy, 2004; Strakowski et al., 2005, 2000a,b, 1998). Our findings appear consistent with the literature, with more than half of our sample having a history of alcohol and/or substance use. The high rate of comorbidity of AU/SU and BP in our sample cannot be adequately explained by diagnostic or ascertainment bias. Fifty of the 101 substance-using participants had a history of AU/SU dating more than 3 weeks prior to their first onset of mania and 40.6% of the entire sample had no comorbid AU/SU despite having relatively severe bipolar disorder. All were experiencing at least their third affective episode.

Our results appear to support the third hypothesis outlined by Strakowski et al. which suggests that the high comorbidity of AU/SU and BP results from various interactions between AU/SU and BP. This hypothesis takes into account varying combinations of factors and causes among individuals, and explains the differences in timing of onset of substance use with relation to onset of bipolar disorder. A small percentage (6.9%) engaged in use after their first onset of mania, indicating that those participants may have used substances in an effort to self-medicate, or as a consequence of mania. Since 49.5% of our alcohol and/or substance-using participants endorsed a history of AU/SU prior to their first onset of mania, and 5 of the 10 participants with immediately preceding use experienced their first episode of mania almost immediately after discontinuing a substance, AU/SU may have contributed to the emergence of BP via some sort of sensitization or kindling process. Finally, the high overall prevalence of SU and BP comorbidity, suggests that some individuals may share common risk factors for SU and BP.

Thirty-four percent of the alcohol and/or substance-using participants engaged in some form of substance use that could not be conclusively categorized as occurring before or after the first onset of mania. This is a particularly heterogeneous group consisting of participants whose substance use would fall into any one of the three other categories if more time-specific information had been available. While the relationship to onset of mania could not be determined in this group, the fact that it comprises 20% of the overall sample adds to the overall prevalence of substance use within our sample.

Alcohol was the substance most frequently used by participants in our sample. Interestingly, more than half of the participants who used alcohol did so at some point prior to their first onset of mania. While this finding would indicate that the bulk of our participants were not using alcohol to self-medicate their symptoms of mania, the possibility remains that they were using alcohol to self-medicate symptoms of depressive episodes which occurred prior to their first onset of mania or to address subsyndromal manic experiences (hypomania or very brief episodes of mania). Further analyses involving the number of depressive episodes prior to the first manic episode might shed more light on this issue.

Forty-eight percent of the substance-using participants engaged in cannabis use, second only to alcohol in frequency of use among our sample. Similar to the results noted for alcohol use, more than half of those using cannabis (65%) did so at some point prior to their first onset of mania. Again, it is possible that these participants were using cannabis to self-medicate depressive symptoms. Duration of cannabis use and duration of manic episodes were not variables for which we had sufficiently precise data to be able to include them in our analyses, so we are unable to link our findings to those reported by Strakowski et al. (2000a,b). However, the fact that the cessation of cannabis use in some patients was directly associated with onset of mania could possibly be explained by the kindling model.

While alcohol and cannabis were the most frequent single substances used, the use of multiple substances, including concurrent substance use and alcohol use, was the most frequent, occurring in 41.6% of the 101 substance-using participants. Interestingly, alcohol was the most common substance used by participants in the immediately preceding, following, and unclear categories, but multiple substance use and/or substance use plus alcohol was most common in the preceding category. Research into the effects of polysubstance use on the number, severity, and course of affective episodes compared to monosubstance use could shed more light on AU/SU and BP comorbidity hypotheses. Of note, the prevalence of cocaine and stimulant use was very low in our study sample relative to what is generally reported for patients with bipolar disorder. This is in all probability related to the exclusion criteria for the MTBD study which included current rapid cycling (4 or more episodes per year), and chronic drug or alcohol abuse. The high frequency of use of alcohol and 'sedative' substances prior to the first mania episode could be in part related to attempts to reduce subthreshold affective (specifically, hypomania or subthreshold mania) instability or to reduce anxiety which is also frequently comorbid with bipolar disorder (Keller, 2006; McElroy et al., 2001; Simon et al., 2004).

In line with findings from the STEP-BD study (Fossey et al., 2006), primary substance use was related with a later age of onset of bipolar disorder. This could be interpreted to mean that there is a subset of individuals with the diathesis for bipolar disorder for whom actual onset of syndromal level disorder requires the stimulus of a psychoactive substance. In depth study of the nature and frequency of alcohol and substance use and its relationship to time of onset of bipolar disorder could help shed more light on the mechanisms through which various substances incite manic and/or depressive symptoms.

While we were able to obtain substance use information on a large percentage of our sample, it is important to note that our findings would likely have been more conclusive had uniform information been available for each participant. In many cases, the information gathered from the life chart and the initial evaluation (PEF) is interchangeable. Both offer information on alcohol and substance use history, previous psychiatric history, and prior hospitalizations. However, in general the PEF focuses more on the history of the patients' present illness, while the life chart focuses more on past events. The life chart is preferable only in that it is more episode specific. The accuracy of both reports often depends on the patient's ability to be a good historian. In the case of our chart review, we were able to gather nearly identical data from both sources. For patients who had both a PEF and a life chart in their record, there were only a few cases in which the sources offered contradictory information. In those cases we utilized the information gathered from the life chart. While we do not feel that the information from one source was necessarily more reliable than the other, we do acknowledge the benefits of having uniform sources available for data collection, and believe our conclusions might have been strengthened from such availability.

Because patients with a significant history of alcohol or substance use were excluded from the MTBD protocol, our sample is particularly selective with regards to comorbid substance use. In light of this fact, it is interesting to see that even though the subjects in our sample did not meet criteria for alcohol or substance abuse at the time of study entry, they still engaged in considerable illicit substance use. This finding sheds light on the pervasiveness of alcohol and substance use even among a population of patients with bipolar disorder who do not meet criteria for substance abuse disorders. It is also interesting to note that our data did not support the findings of the NCS which reported that a mental disorder generally precedes an addictive disorder in people with a history of both (Kessler et al., 1996). The fact that more than half of our sample engaged in alcohol or substance use prior to the onset of mania is likely a function of the subthreshold nature of their substance use, in contrast to meeting the diagnostic criteria for addictive disorders used in the NCS.

In sum, our findings support earlier reports of the high prevalence of substance use among patients with bipolar disorder. Treatments targeting comorbid AU/SU and BP are clearly needed, as are prophylactic treatments targeting adolescents and young adults who are at increased risk for BP and/or alcohol and substance use disorders. At the very least, individuals with BP and AU/SU should be provided with psychoeducation concerning the bi-directional influence of alcohol and substance use and its relationship to onset, course, and prognosis of bipolar disorder.

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